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Mathematical approach for modeling the uterine electrical activity

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Abstract

The aim of physiological modeling of the uterine electrical activity generated at cellular level is to understand the main physiological uterine contractile mechanisms, in particular, the propagation mechanisms and their relationship with the uterine EMG signal recorded externally from the abdominal wall of the pregnant women. In this present paper, we model the electrical activity simulated at its cellular level. This model is built in three steps: first we built a model based on the formulation of Hodgkin and Huxley and adapted to the specificities of the uterine cell. The second step was the integration of the cellular model in a two-dimensional propagation model by using the reaction-diffusion equations in order to simulate the propagation of the uterine activity at the tissue level. Finally, a simplified version of the space-time integration of the electrical activity was used to build a first example of the uterine EMG.

Keywords: Electrophysiological model; Uterine Electromyogram (EMG); Reaction-diffusion equations

I. Introduction

Spontaneous preterm labor is clinically defined as the presence of regular uterine contractions that occur before 37 weeks of gestation and are associated with effacement and dilation of the cervix prior to term gestation [1-4]. Preterm birth accounts for 75% of early neonatal morbidity and mortality and the half of long term infant mortality [1]. The efficiency of interventions to prevent preterm birth has been disappointing [2, 5].

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There is no effective treatment for preterm labor yet nor a single test to accurately predict preterm birth [6-7]. This is mainly due to the fact that it is often difficult to diagnose preterm labor because its symptoms and signs occur commonly in normal women who do not deliver preterm. Therefore, much work has to be done in order to improve preterm labor detection.

Labor occurs due to regular uterine contractions causing the dilatation of the cervix and the expulsion of the fetus. Uterine contractions leading to labor are triggered by synchronized electrical waves through the uterine musculature, the myometrium. It was demonstrated that the evolution of the uterine contractions from weak and localized during pregnancy to strong and propagated is due to an increase of the excitability and the propagation of the electrical activity. It was therefore reported that the analysis of this electrical activity can provide valuable information about contractions in obstetric monitoring [8-11]. The recorded signal, called the uterine electromyogram (EMG), is the bioelectrical signal associated with the uterine electrical activity. Therefore, uterine EMG was widely investigated in order to predict the risk of preterm labor and subsequent preterm birth [12-13]. In spite of very exciting result, this technique is not currently used in routine practice due to the insufficient preterm labor detection ratio for clinical use. A thorough understanding of the mechanism by which labor is initiated is of vital importance in order to develop a rational approach towards improving true labor detection.

Modeling the electrical activity in uterine tissue is an important step to promote deep understanding of the physiological uterine contractile mechanisms. The question of modeling the uterine electrical activity has been widely approached by many research groups for different purposes. Their aim is, generally, to better understand the relationships between internal physical, biological, or physiological characteristics and external parameters extracted from signal recordings. Vauge et al. [17] developed a simple mathematical model with three physiologically significant states (quiescent, contracted, and refractory) to describe the changes in intrauterine pressure associated with a contraction during human parturition. Bursztyn2007 et al. [3] presented a mathematical model of myometrial smooth muscle cells contraction developed to study the process of excitation and contraction. Moreover, Rihana et al. developed an electrophysiological model of the uterine electromyogram based on physiological data from its genesis at cellular level, to its propagation to the tissue level. More recently, Rabotti et al. [18] proposed a five-parameter analytical model of the uterine EMG volume conductor and the cellular action potential (AP), the model was tested on uterine EMG signals recorded by a grid of 64 high-density electrodes.

The focus of this paper is to present a new mathematical approach for modeling the uterine electrical activity. The parameters in the mathematical equations describe the underlying physiological phenomena of the uterine activity (excitability and propagation). By modifying the values of these parameters, we will be able to generate synthetic signals corresponding to various physiological states of the uterus (pregnancy, labor at term) and therefore, identify the tools that are best suited to extract physiological information.

In the present paper, a novelty lies in the use of a multilayer modeling of the uterine electrical activity starting from its source (at the cellular level), and its propagation at the tissue level (the myometrium), then through the abdomen.

II. Methods

Like all excitable cells, uterine cells (myocytes) present during pregnancy a resting potential oscillating around -50 mV. When resting potential reaches a certain threshold, it triggers a burst of action potentials. The shape and characteristics of the uterine electrical activity vary during pregnancy from a single spike, an irregular train of action potentials, to a regular train of action potentials observed at the end of term. These different types of activity result from the different kinetic parameters involved in the ionic exchange related to the cellular excitability. The flow of the ionic currents through the membrane of

the uterine cell charges or discharges the capacity of the membrane. For a unit of surface of the membrane, the current exchanges are given by the following formula:

$$\frac{dV_m}{dt} = \frac{I_{stim} - \sum_i I_i}{C_m} \quad (1)$$

where C_m is the capacity of the membrane, V_m is the potential of the membrane, I_{stim} is the stimulation current and $I_{ionic} = \sum_i Ii$ is the density of the current of the membrane. I_{ionic} represents the sum of the current densities going in and out of the cell. For a uterine cell, I_i includes the Sodium voltage dependant current, Calcium voltage dependant current, Potassium voltage dependant current, Potassium-calcium dependant current as well as the leakage current I_l (associated mainly to Chlorine ions).

$$I_i = G_i m_i^x h_i^y (V_m - E_i) \quad (2)$$

Where G_i is the maximum conductance for a given ion i, m_i and h_i are the dynamic variables representing the activation and inactivation gates of the ionic channels, respectively, x et y are the numbers of these gates. E_i is the Nernst potential of the associated ion. The temporal variations of these gates are expressed by a first order ordinary differential equation [14]. Furthermore, it is well known that calcium plays an important role in the excitation-contraction coupling of the uterine cell. Therefore, we added an ordinary differential equation (3) in order to describe the temporal behavior of the intracellular concentration of calcium.

$$d[Ca^{2+}]_i/dt = f_c(\alpha I_{Ca} - K_{Ca}[Ca^{2+}]_i) \quad (3)$$

Where f_c is the participation ratio to the cytosolic concentration of Calcium, α is a factor that allows the conversion of the calcium current into cytosolic concentration, and K_{ca} is a constant representing the effect of the extraction of calcium to the extracellular medium, of diffusion and storage of calcium in the intracellular environment.

The complete system that describes the cellular activity is presented by the equation system (4). The numerical integration of the system allows to obtain the temporal variations of the membrane's potential V_m. The different types of activities recorded during pregnancy can be simulated by using the suitable set of parameters. The values of the obtained parameters can then be represented with respect to physiological phenomena.

II.2 – Dynamic analysis of the model

The model can be seen as a dynamical nonlinear system where small changes in parameters can produce drastic changes in its response. It is important therefore to systematically analyze the influence of all parameters in order to determine for each one the range of the physiological value. For this aim, we have used the bifurcation analysis, a technique classically used in neuroscience [15]. Therefore, the oscillations at the end of term are seen as stable limit cycles of the model. By analyzing the bifurcation diagrams, we studied the parameters that can induce the regular bursts of action potential representative of the electrical activity at the end of term or labor.

$$\begin{cases} dV/dt = (I_{stim} - I_{ion}(V, m_{Ca}, h_{1Ca}, h_{2Ca}, n_K, [Ca^{2+}]_i))/C_m \\ dm_{Na}/dt = (m_{Na\infty}(V) - m_{Na})/\tau_{mNa}(V) \\ dh_{Na}/dt = (h_{Na\infty}(V) - h_{Na})/\tau_{hNa}(V) \\ dm_{Ca}/dt = (m_{Ca\infty}(V) - m_{Ca})/\tau_{mCa}(V) \\ dh_{1Ca}/dt = (h_{Ca\infty}(V) - h_{1Ca})/\tau_{h1Ca}(V) \\ dh_{2Ca}/dt = (h_{Ca\infty}(V) - h_{2Ca})/\tau_{h2Ca}(V) \\ dn_{k1}/dt = (n_{k1\infty}(V) - n_{k1})/\tau_{nk1}(V) \\ dn_{k2}/dt = (n_{k2\infty}(V) - n_{k2})/\tau_{nk2}(V) \\ dh_{k1}/dt = (h_{k1\infty}(V) - h_{k1})/\tau_{k1}(V) \\ d[Ca^{2+}]_i/dt = f_c(\alpha I_{Ca}(V, m_{Ca}, h_{1Ca}, h_{2Ca}, [Ca^{2+}]_i) - K_{Ca}[Ca^{2+}]_i) \end{cases} \quad (4)$$

The nonlinear system describing the electrical activity can be described by the following equation:

$$\dot{z} = f(z, p) \quad (5)$$

Where z is the vector representing the model's variables, $\dot{z}$ represents the temporal variation of these parameters and p represents the parameters. The stable state of the system id reached when $\dot{z} = 0$. There exist different types of the stable states. In the present work, we will study the attractors which represent the points where the uterine cell presents a stable membrane potential, as well as the unstable limit cycles where the cell has an oscillating-type response.

II.3 – Cellular propagation model and reconstruction of the EHG

Since the myometrium exhibits cable like properties [16], we have therefore used the monodomain model, classically applied on cardiac muscles, in order to simulate the propagation. The propagation of uterine electrical activity can be represented by the reaction-diffusion equation:

$$\frac{\partial V_m}{\partial t} = \frac{I_{stim} - \sum_i I_{ion}}{C_m} + \frac{D\nabla^2 V_m}{A_m C_m} \quad (6)$$

where D represents the diffusion tensor. Knowing that the uterine tissue can present, due to its structure, privileged directions of propagation (longitudinal and transversal), D can be reduced to a diagonal matrix. We suppose at first that the propagation in homogeneous with

$$D_x = 1/C_m R_{ax} \quad (7)$$

and

$$D_y = 1/C_m R_{ay} \quad (8)$$

where R_{ax} and R_{ay} represents the longitudinal and transverse resistances, respectively. This equation is illustrated by figure 1. Then, we simulated the electrical activity at the abdomen surface simply by integrating the electrical activities of all the considered cells in terms of the distance between the cell and

the recording point. This approach is very simplistic but provides a first representation of the uterine EMG signal. The mechanical activity associated to the electrical activity is estimated as proportional to the number of active cells at any given time.

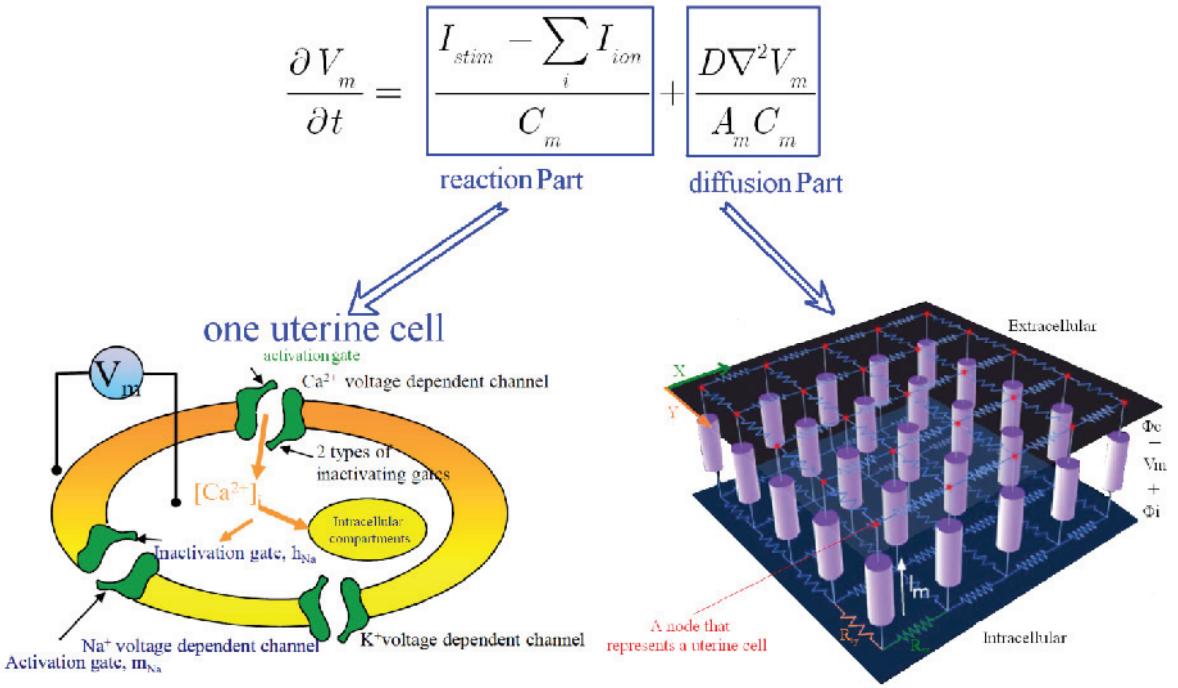

Fig. 1. Reaction-diffusion equation

III – Results:

The cellular model we have just described will allow reproducing different types of uterine activities that can be observed during pregnancy. Figure 2 represents different shapes of uterine electrical activity.

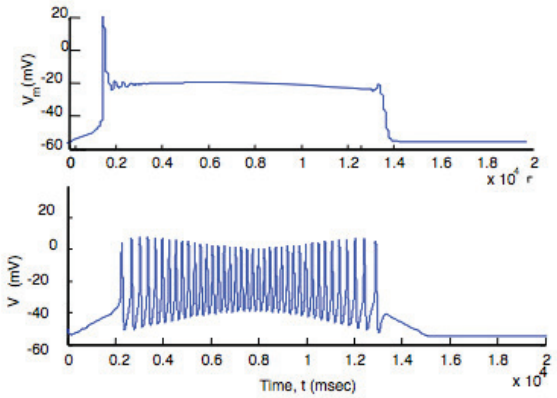

Fig. 2. Two different types of electrical activity simulated by the model: (a) plateau-bursting electrical activity obtained at mid-pregnancy, (b) regular burst of action potential as observed at labor.

In figure 2.a, the model response shows a plateau-bursting electrical activity obtained at mid-pregnancy. Moreover, figure 2.b illustrates a regular burst of action potentials at labor.

The bifurcation analysis allowed us to obtain the range values of the parameters suitable for the simulation of the different physiological responses and to study the effect of different tocolytic agents. For example, increasing the calcium conductance allows to open calcium channels and initiating the onset of bursts of AP, while its reduction inhibits burst-type response (Fig.3). This justifies the use of products that decrease the calcium conductance (calcium blocker) as tocolytic agents.

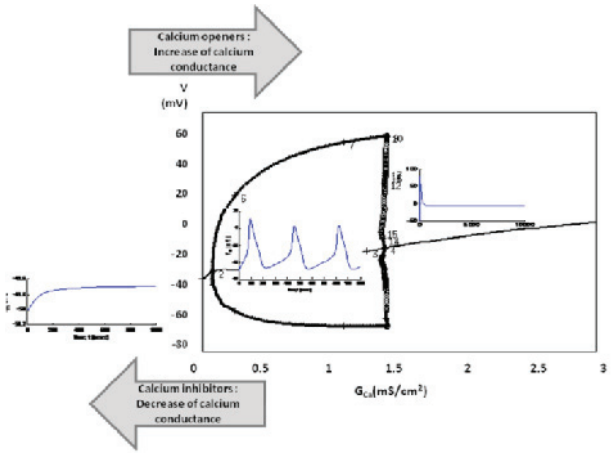

Fig. 3. the model's response: V_m in terms of calcium conductance

Furthermore, figure 4 shows two bursts of uterine EMG signals simulated by a sinusoidal stimulation current and the associated mechanical activity.

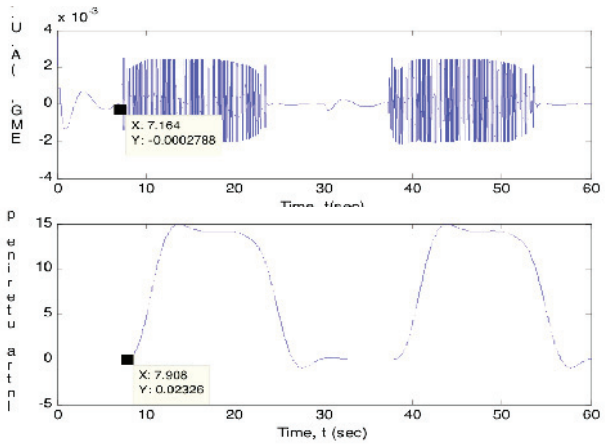

Fig. 4. (a) Simulated uterine EMG signals; (b) The associated mechanical activity

IV – Discussion and Conclusion:

In the present paper, we described a first approach for multilevel modelling of uterine EMG signals, from its source at the cellular level to its propagation on the surface of the myometrium. Like all models, our proposed model presents some limitations primarily related to the simplifications used. Future work will focus on overcoming these major limitations, mainly related to the propagation at the tissue level.

The present work opens new perspectives for improving the current results. We are currently working on developing a more realistic 3D structure of the areas of conduction including the conductor volume.

Regarding the modeling of the propagation, it would be interesting to deepen the study at the tissue level in order to define the position, the percentage and the number of pacemaker areas in the uterine tissue, as well as the distribution of gap junctions as well as the orientation of the fiber uterine (fiber bundles), not to mention the phenomenon of wave propagation of calcium. Moreover, in order to study the abdominal level, it would be necessary to develop new approaches to move from tissue level *(uterine EMG)* into the organ level *(surface uterine EMG)*, without being confronted by the calculation time and complexity of the current model. More studies have to be also done on a real conductor volume (fat layer, skin layer and visceral tissue layer). These developments will be coupled with experimental multilevel (tissu, organ, abdomen), on different animal species, as well as pregnant women, in order to extract from the experimental data the necessary parameters for developing the model then for its validation once it is developed.

The simulation of the signal at the abdominal level will then link all the various phenomena involved in uterine contractility (normal or pathological) to the uterine EMG signal, the only signal used for future clinical applications in order to refine the processing tools of the uterine EMG signal used to detect at early stage and reliably preterm labor.

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